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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/489,850	01/24/2000	Diane Van Alstyne	51916/107	6341

7590 12/18/2006

Insight Biotek Inc.
Diane V. Alstyne
465 Stony Point Rd.
Suite 115
Santa Rosa, CA 95401

EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	PAPER NUMBER
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/18/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/489,850	ALSTYNE ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The response filed 3-2-06 has been entered into the record.

Specification

A substitute specification including the text and changes of the preliminary amendment filed 1-24-00 is required pursuant to 37 CFR 1.125(a) because: the preliminary amendment filed 1-24-00 could not be entered in multiple instances because they requested line numbers did not contain the recited textual material.

A substitute specification must not contain new matter. The substitute specification must be submitted with markings showing all the changes relative to the immediate prior version of the specification of record. The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. An accompanying clean version (without markings) and a statement that the substitute specification contains no new matter must also be supplied. Numbering the paragraphs of the specification of record is not considered a change that must be shown.

Priority

It is noted that this application appears to claim subject matter disclosed in three prior Applications. The current status of all non-provisional parent applications referenced should be updated.

Drawings

The proposed drawings corrections in this application have been accepted. ***The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.***

Specification

The title of the invention is not descriptive of the now claimed invention. A new title is required that is clearly indicative of the invention to which the claims are directed.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration filed 3-2-06 is defective because it is not executed by inventor Diane Van Alstyne.

Information Disclosure Statement

No information disclosure statement has been filed in this application.

Election/Restrictions

Applicant's election of Group II, Specie F, SEQ ID NO:20 in the response of 3-2-06 is acknowledged. ***Upon reconsideration, the restriction requirement between Groups I and II is withdrawn. The specie election is maintained.*** Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Objections

Claims 16 is objected to because of the following informalities: the independent claim recites the acronym "MRHAS" that is not first defined in the independent claim. While acronyms are permitted in the claims, they must be fully defined in any independent claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As to claims 14, 15, 18, 19, 20, 22 and 23, the claims are drawn to a protective effect *in vivo* against challenge to comprising administering an "effective amount" of a composition comprising a monoclonal antibody or binding fragment thereof that binds a meningitis related homologous antigenic sequence (MRHAS) shared by viral and/or

bacterial meningitis etiological agents. The claims are interpreted as prevention of infection as protection indicates prevention of infection or disease (see specification page 76, lines 15-22).

As to claims 16, 17, 21, 24 and 25, the claims are drawn to treating a patient infected with a meningitis etiological virus and/or bacteria to significantly clear said virus and/or bacteria comprising administering a therapeutically effective amount of a composition comprising a monoclonal antibody or binding fragment thereof that binds a meningitis related homologous antigenic sequence (MRHAS) shared by viral and/or bacterial meningitis etiological agents. Treatment encompasses curing or easing symptoms (see MSN Encarta Dictionary).

The sole teaching of the specification are drawn to an assessment of the ability of the monoclonal antibody SP8, produced by the cell line 11E-1 to reduce bacteremia in a challenge model and also a study of the survival rate (see pages 74-78, Example 4). In the instant case the monoclonal antibody binds the sequence QQPPE in *S. pneumoniae* and the animals were challenged with *H. influenzae* that has the homologous sequence QVQNNKP. The antibody was first provided to the animal and then after 24 hours the animals were challenged with the *H. influenzae*. Table 10 indicates that while the monoclonal antibody reduced the number of bacteria in the blood when administered prior to exposure, so did the negative control and the positive control. The specification teaches single RV1 monoclonal antibody that defines family of homologous cross-reacting septapeptide antigens in viruses and bacteria known to cause meningitis (see pages 31-33). The specification lacks any description of any *in vitro* assay of biological activity for the monoclonal antibody RV1. The specification does not teach that clearing etiological agents provide for "curing or easing symptoms" as clearly encompassed by the term "treating" and does not teach protection from in vivo challenge for the following reasons.

At the time that the invention was made, none of the disclosed antigens were known or demonstrated by the specification to provide active immunity or protective antibodies

thereto to provide passive immunity against the cognate disease or disorder, much less a heterologous disease or disorder for which the antibody is cross-reactive. The ability of an antigen to bind an antibody or the ability of the antibody to recognize its cognate antigen is not recognized by the art to demonstrate therapeutic efficacy of a vaccine or antibody. Many references teach that the presence of antibody or ability to generate an antibody does not correlate with efficacy. Applicants are essentially claiming passive immunization as opposed to active immunization and as such, the antibody must have the claimed properties. There is absolutely no demonstration of protective immunity upon administration in any animal model of disease. The art is replete with evidence that the ability to produce an antibody (immunogenicity) is insufficient to correlate with protection from infection. See for example Feng et al (Infection and Immunity, 64(1):363-365, 1996) that teaches that P55, is an immunogenic but nonprotective 55-kilodalton *Borrelia burdorferi* protein in murine lyme disease. It is well recognized in the vaccine art, that it is unclear whether an antigen(s) derived from a pathogen will elicit protective immunity. Ellis, R.W. (Chapter 29 of "VACCINES" [Plotkin, S.A. et al. (eds) published by W. B. Saunders company (Philadelphia) in 1988, especially page 571, 2nd full paragraph] exemplifies this problem in the recitation that "The key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.... and thus protect the host against attack by the pathogen". The specification fails to teach even one monoclonal antibody alone or in combination with other antibodies does in fact confer protection from infection (*in vivo* challenge) or have some recognized therapeutic efficacy (treatment), as is required by the claimed invention. The art in 2001 clearly recognized that the ability to produce an antibody does not correlate with protection from infection (Chandrashekar et al US Patent NO. 6,248,329 column 1, lines 35-40). Therefore, the fact that an antibody binds the antigen, does not provide any indication of the usefulness of the antibody in protection from infection. As such, one skilled in the art would have

ample reasons to doubt the ability to use a composition comprising the monoclonal RV1 antibody as a passively immunizing vaccine. Similarly, there is no evidence that any of the antibodies provide for treatment of infection post exposure by any bacteria or virus. For rubella in particular, the art recognizes no efficacy of post-exposure passive immunization (see Public Health Agency of Canada: Vaccine-Preventable Diseases Rubella, page 12, passive immunization).

Applicants characterize that in severe meningoccoal infections bacteremia, petechiae and shock may develop (see page 2, lines 15-20). The skilled artisan also readily recognizes that blood is a sterile body fluid. Bacteria present in the blood provide for a disease state called bacteremia. The fact that all the animals in Example 4 bacteria in the blood, indicates that the monoclonal antibody cannot protect from challenge *in vivo* and that all the animals progressed from a peritoneal infection to a blood infection. So, the antibody even when administered 24 hours in advance the monoclonal antibody cannot protect. Further, the specification speculates that the protective effect may block the common MRHAS-mediated entry of the meningitis organisms into carrier monocytes (see specification page 17, lines 30-38). The specification does not teach protection from infection because all of the animals with all antibodies clearly have bacteria in blood 24 hours after inoculation into the peritoneum. Therefore, it is clear that the bacteria survived and moved from the peritoneum into the blood and infection is not prevented or protection from challenge not achieved. There is no demonstration of any *in vitro* activity of any other anti-bacterial monoclonal antibody that is correlative or predictive of protection *in vivo* against any other disclosed bacterial antigen as claimed. There is no demonstration of any *in vitro* activity that provides for in vivo efficacy (cure or alleviation of symptoms or protection from infection) with respect to treatment of any patient infected with a meningitis etiological agent as claimed. There is no evidence of clearance of the agent provides for treatment as claimed. Treatment is conventionally defied as a procedure, or technique for curing or alleviating a disease, injury, or condition. There is no

evidence that any monoclonal antibody, even those that promote clearance of bacteria or viruses alleviate the disease or condition of the patient for the reasons set forth below. Additionally, the specification fails to disclose that the RV1 or SP8 monoclonal antibody provides for protection against any viral meningitis agents using *in vitro* or *in vivo* assays that correlate with protection from *in vivo* challenge. In particular, the specification contemplates protection from HIV using the RV1 monoclonal antibody. It has been well known in the art that retroviral infections in general, and HIV infections in particular, are refractory to anti-viral therapies. The obstacles to therapy of HIV are well documented in the literature. These obstacles include: 1) the extensive genomic diversity and mutation rate associated with the HIV retrovirus, particularly with respect to the gene encoding the envelope protein; 2) the fact that the modes of viral transmission include both virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert manner, as well as via free virus transmission; 3) the existence of a latent form of the virus; 4) the ability of the virus to evade immune responses in the central nervous system due to the blood-brain barrier; and 5) the complexity and variation of the pathology of HIV infection in different individuals. The existence of these obstacles establish that the contemporary knowledge in the art would not allow one skilled in the art to use the claimed invention with a reasonable expectation of success and without undue experimentation. Further, it has been well known in the art that individuals infected with HIV produce neutralizing antibodies to the virus, yet these antibodies are not protective and do not prevent the infection from progressing to its lethal conclusion. Further, as taught by Fahey et al. (Clin. Exp. Immunol. 88: 1-5, 1991) , clinical trials using a variety of immunologically based therapies have not yielded successful results in the treatment and/or prevention of HIV infection (see Table 1). Fahey et al. also disclose in vitro-in vivo discrepancy involved in applying Receptor-Directed Treatments involving CD4-specific inhibitors (see page 3, column 1). Fahey et al. discloses that monoclonal antibody therapies have not provided any clinical benefits and "it is not clear how adding these

additional antibodies would make a difference" (see page 3, second column, third full paragraph). In support, Daar et al. (PNAS 87: 6574-6578, 1990) discloses high concentrations of soluble CD4 required for neutralizing infection poses a formidable problem for such treatment of HIV-1 infection in vivo (see entire document including Abstract and Discussion). Haynes et al. (Science 271: 324-328, 1996) also teaches the limitations of protective immunity to HIV infection, including that "Current animal models of either HIV or simian immunodeficiency virus (SIV) fall short of precisely mirroring human HIV infection" and that "lacking these models, researchers must turn towards human clinical trials to answer many of the difficult questions about HIV pathogenesis and HIV vaccine development" (see page 40, column one, third paragraph). Fox (Biotechnology 12: 128, 1994) also discloses that ability to treat and/or prevent HIV infection is highly unpredictable and has met with very little success. Sommerfelt et al. (J. Gen. Virol. 76: 1345-1352, 1995) discloses that certain antibodies directed against CD18, CD11b and CD11c inhibited HIV-1 induced syncytium formation but not entry (Abstract). Also, certain anti-ICAM-3 antibodies inhibited HIV-1 specific entry but not syncytium formation and only one antibody inhibited HIV-1 induced syncytium formation , entry and infectivity under in vitro conditions (Abstract and Results). Here, it is noted that inhibition was not complete under in vitro conditions using cell lines. Also, Sommerfelt et al. disclose that the inhibitory anti-adhesion antibodies varied on the cell type tested as well as the type of assay (see Results and Discussion). In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective methods to suppress the infection of leukocytes with HIV wherein said method comprises administering to a subject exposed to or infected by HIV, including the use of adhesion-based reagents, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed

methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for suppressing HIV infection *in vivo*.

The specification fails to provide any written description of *in vivo* activity for a monoclonal antibody (RV1 or SP8) or any other monoclonal antibody as claimed that is protective for in vivo challenge, curative or alleviates symptoms of disease or disorder as claimed.

In view of the state of the art with respect to use of monoclonal antibodies for therapeutic in 1993, the unpredictability of the art as it relates to correlating antigenicity with protection from infection and the lack of either *in vitro* assays that correlate with *in vivo* efficacy or *in vivo* models that correlate with efficacy for treatment, it would require undue experimentation on the part of the skilled artisan to use the monoclonal antibodies for *in vivo* therapeutics (cure or alleviate) and protection from infection as claimed.

Claim 14-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

16, 17, 21, 24 and 25, are indefinite in the use of the term "effective amount" because it is unclear what amount is effective for (i.e. the result variable). Further, the specification does not define or determine or teach an "effective amount". Effective amounts of monoclonal antibodies were not established in the art at the time that this invention was made. Monoclonal antibodies were not in routine clinical use at the time that this invention was made. As such, the skilled artisan would be unable to determine the metes and bounds of the "effective amount".

As to claims 16, 17, 21, 24 and 25, the claims are prima facie indefinite in the use of the term "therapeutically effective amount" because the therapeutic outcome is not defined in the specification or claimed. The specification does not teach what symptoms are treated. The art at the time in 1993 does not teach therapeutically effective amounts

of monoclonal antibodies. Monoclonal antibodies were not in routine clinical use at the time that this invention was made. As such, the skilled artisan would be unable to determine the metes and bounds of the "effective amount".

Status of the Claims

All claims stand rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Examiner Jeffrey Siew can be reached on 571-272-0787.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patricia A. Duffy, Ph.D.
Primary Examiner
Art Unit 1645